PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference NEREUS.091VP	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2005/014846	International filing date *(day/month/year)* 29 April 2005 (29.04.2005)	Priority date *(day/month/year)* 30 April 2004 (30.04.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant NEREUS PHARMACEUTICALS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 23 January 2007 (23.01.2007)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yoshiko Kuwahara e-mail: pt07@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/014846	29.04.2005	30.04.2004

International Patent Classification (IPC) or both national classification and IPC
INV. C07D491/04 C07D207/12 C07F5/02 A61K31/407

Applicant
NERUES PHARMACEUTICALS, INC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Jeanjean, Fabien Telephone No. +49 89 2399-2920

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/014846

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-2 (part), 3-4, 5-7 (part), 8, 9-12 (part), 13-17, 18-19 (part), 20, 21-24 (part), 25-27, 28-30 (part), 31-36, 37-38 (part), 39-51 (industrial applicability), 52, 53-61 (industrial applicability), 62-63 (part), 64 (industrial applicability)

because:

☒ the said international application, or the said claims Nos. 39-51, 53-61, 64 (industrial applicability) relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1-2 (part), 3-4, 5-7 (part), 8, 9-12 (part), 13-17, 18-19 (part), 20, 21-24 (part), 25-27, 28-30 (part), 31-36, 37-51 (part), 52, 53-64 (part),

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-2, 5-7, 9-12, 18-19, 21-24, 28-30, 37-51, 53-64 (all part)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-2, 5-7, 9-12, 18-19, 21-24, 28-30, 37-51, 53-64 (all part)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-2, 5-7, 9-12, 18-19, 21-24, 28-30, 37-51, 53-64 (all part)
Industrial applicability (IA)	Yes:	Claims	1-2, 5-7, 9-12, 18-19, 21-24, 28-30, 37-38, 62-63 (all part)
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III.

Claims 39 to 51, 53 to 61, 64 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV.

The separate inventions are:

This Authority considers that there are 5 inventions covered by the claims indicated as follows:

I: Claims 1 to 2, 5 to 7, 9 to 12, 18 to 19, 21 to 24, 28 to 30, 37 to 51, 53 to 64 (all part) related to the compounds of formula I in which R_3 is a halogen, their compositions and the use thereof

II: Claims 1 (part), 4, 5 to 12 (part), 13, 14, 16, 17, 18 to 19 (part), 20, 21 to 30 (part), 31 to 33, 37 to 51 (part), 52, 53 to 64 (part) related to the compounds of formula I in which R_3 is a methyl and R_2 comprises at least a cycle, their compositions and the use thereof

III Claims 1 to 2 (part), 3, 5 to 10 (part), 21 to 27 (part), 37 to 51 (part), 53 to 64 (part), related to the compounds of formula I in which R_3 is a methyl and R_2 does not comprise a cycle, their compositions and the use thereof

IV: Claims 1 to 2, 5 to 7, 9 to 12, 18 to 19, 21 to 24 , 28 to 30, 37 to 51, 53 to 64 (all part) related to the compounds of formula I in which R_3 is a C_2-C_{24} alkyl, unsaturated C_2-C_{24} alkenyl, unsaturated C_2-C_{24}, acyl, acyloxy, alkyloxycarbonyloxy, aryloxycarbonyloxy, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, aryl, heteroaryl, arylalkoxy carbonyl, alkoxy carbonylacyl, phenyl, cycloalkylacyl, alkylthio, arylthio, carboxy and halogenated alkyl including polyhalogenated alkyl, hydroxy, oxysulfonyl, amino, aminocarbonyl, aminocarboyloxy, nitro, azido, cyano their compositions and the use thereof.

V: Claims 34 to 36 related to the compounds of formula VI, their compositions and the use thereof

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

The closest prior art for the present application is represented by D1 disclosing the salinosporamide A which exhibits potent cancer cell cytoxicity and appears to be a 20S proteasome inhibitor (see p. 355, scheme 1). This compound is excluded by the applicant with a proviso. According to D2 the 20S complex is the proteolytic core of a 26S complex that degrades or processes ubiquitin-conjugated proteins (see p. 1, l. 16 to 17)). Furthermore proteasome inhibitors block IkB-α degradation and activation of Nf-kB (see p. 3, l 3 to 4).

The technical problem underlying the present claims is seen as the provision of further compounds for the treatment of cancer and other proteasome or Nf-kB related disorders.

In view of the above mentioned compounds of D1, the different groups of compounds related to the above-mentioned inventions do not share a common special technical feature as required by rule 13.2 PCT. Therefore the application lacks of unity of invention (Rule 13.1 PCT).
Only the first invention has been searched.

Re Item V.
Reasoned statement with regard to novelty, inventive step or industrial applicability on the first invention; citations and explanations supporting such statement

1 Reference is made to the following document:

D1 : "Salinosporamide A: A Highly Cytotoxic Proteasome Inhibitor from a Novel Microbial Source, a Marine Bacterium of the New Genus *Salinospora*", Feling R. H., Buchanan G. O., Mincer T. J., Kauffman C. A., Jensen, P. R., Fenical W., *Angewandte Chemie International Edition*, **2003**, *42*, 3, 355-357
D2 : WO9915183

2 Novelty

2.1 The subject-matter of claims 1 to 2, 5 to 7, 9 to 12, 18 to 19, 21 to 24, 28 to 30, 37 to 51, 53 to 64 (all part) appears to be new in the sense of Article 33(2) PCT.

2.2 The document D1 discloses (the references in parentheses applying to this document): the salinosporamide A (p. 355, scheme 1, compound 1) which is excluded with a proviso by the applicant from the scope of formula I.
The compound of formula I of claim 1 and of the dependent claims 2, 5 to 7, 9 to 12, 18 to 19, 21 to 24, 28 to 30 appears to be new vis-à-vis D1.
The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding claims 37 to 51, 53 to 64 which therefore are also considered new vis-à-vis D1.

2.3 The document D2 discloses (the references in parentheses applying to this document): the compounds 3a to 3e (p. 18, scheme 2). The compounds of the present application differ in that R_3 cannot represent a hydrogen.
The compound of formula I of claim 1 and of the dependent claims 2, 5 to 7, 9 to 12, 18 to 19, 21 to 24, 28 to 30 appears to be new vis-à-vis D2.
The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding claims 37 to 51, 53 to 64 which therefore are also considered new vis-à-vis D2.

3 Inventive step

3.1 The present application appears to not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 2, 5 to 7, 9 to 12, 18 to 19, 21 to 24, 28 to 30, 37 to 51, 53 to 64 (all part) does not involve an inventive step in the sense of Article 33(3) PCT.

3.2 The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses (the references in parentheses applying to this document): salinosporamide A (p. 355, cpd. 1, scheme 1) which exhibits potent cancer cell cytotoxicity and appears to exert its cytotoxic effects through inhibition of the 20S proteasome (p. 355). The compounds of the first invention differ in that R_3 is a halogen instead of a methyl.

The problem to be solved by the present invention may therefore be regarded as the provision of further compounds inhibitor of proteasome for the treatment of cancer.
There are no examples in the description of compounds of the first invention showing an inhibition of proteasome. It seems that the compounds of the first invention do not solve the problem above mentioned. An inventive step cannot therefore acknowledged for the compounds of claim 1 and the dependent claims 2, 5 to 7, 9 to 12, 18 to 19, 21 to 24, 28 to 30.
The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding claims 37 to 51, 53 to 64 which therefore are also considered not inventive.

Remarks

1 The term "prodrug" used in claims 1, 5, 25, 31, 39, 44, 46, 47, 50, 53, 60 to 63 is considered unclear. The person skilled in the art is left to an undue burden when he has to decide which compounds are encompassed by the term prodrug.

2 The term "variant" used in claims 1, 5, 25 and 31 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim/s unclear, Article 6 PCT.

3 There is an obvious error in claims 36, 37, 39, 44, 46, 47, 48, and 50 wherein the claimed pharmaceutical composition (or methods) comprises (or use) a compound of claims 46 and 49 (related to methods).

4 The terms "alkyl", "alkenyl", "alkoxy" are defined in the description (see p. 72, par. 298) as a "unsubstituted or substituted" hydrocarbon or ether. This definition does not correspond to the common meaning given for these terms in organic chemistry. This inconsistency between the description an the claims has to be removed.

5 The vague and imprecise statement "spirit of invention" in the description on page156 (par 510 and 511) implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.

6 The statement "the invention illustratively described herein suitably can be

practised in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein" lets the impression that not all the technical features for performing the invention are disclosed. It seems therefore that there is a lack of disclosure of the present invention.

7 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor are this document identified therein.